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10/579,712	01/03/2007	Edouard Guy Stanley	DVCC-009	5098

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EXAMINER

MONTANARI, DAVID A

ART UNIT	PAPER NUMBER
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1632

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/579,712	Applicant(s) STANLEY ET AL.
	Examiner DAVID A. MONTANARI	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 June 2011.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 41-66 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 41-66 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)</p> <p>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date _____.</p> | <p>4) <input type="checkbox"/> Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.</p> <p>5) <input type="checkbox"/> Notice of Informal Patent Application</p> <p>6) <input type="checkbox"/> Other: _____.</p> |
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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/7/2011 has been entered.

1. Claims 41, 53, 54, 56-58 and 65 are amended.
2. Claim 66 is new.
3. The rejection of claims 57 and 65 under 35 USC 112, 1st parag. new matter is withdrawn in view of Applicant's amendments to the claims.
4. The rejection of claims 54-65 under 35 USC 112, 2nd parag. is withdrawn in view of Applicant's amendments to the claims.
5. The rejection of claims 41-50 under 35 USC 102(e) is withdrawn in view of Applicant's amendments and argument that Thomson et al. does not teach individually separate hESC's prior to centrifugation.
6. The rejection of claims 41 and 50-53 under 35 USC 103(a) is withdrawn in view of Applicant's amendments and argument that Thomson et al. does not teach individually separate hESC's prior to centrifugation.
7. The rejection of claims 54, 55, 56 and 59-65 under 35 USC 103(a) has been withdrawn in view of Thomson teaching non-individual separate hESCs.

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8. Claims 41-66 are examined in the instant application.

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/523,249, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

A search of 60/523,249, from which the instant application depends, provides no support for the limitations of centrifuging hES cells at 1500 rpm for 2 minutes at 4°C as recited in claim 57. A search of 60/523,240 provides no recitation of any RPM, time or temperature for the centrifugation of hES cells. However a search of PCT/AU04/01593 does provide support for the limitations of 1500 rpm for 2 minutes at 4°C as recited in claim 57 and thus priority is given to 11/19/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 41 is newly amended to recite that the suspension obtained using the claimed method will comprise "individual separate" hESCs. Applicant, in their arguments, cites pg. 22 lines 3-6 as providing support for this new claim limitation. However a review of the cited page and line numbers, the originally filed claims and the specification as a whole, does not provide support for a suspension of individually separate hESCs. While a cell count may have been performed following re-suspension of the hESCs, the mere fact that a cell count was performed does not provide the support that all hESCs that are in suspension are in fact individually separate without the presence of clumps or 2-3 cell collections of hESCs. While the ordinary artisan may appreciate that a representative number of cells should be separate to provide an approximate cell count, clumps will in fact remain, thus while a cell count was performed this does not provide the necessary support in the specification that hESCs cells in suspension are individually separate.

Claims 41-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of forming hESC aggregates comprising obtaining a

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suspension of hESCs, wherein said suspension comprises clumps and single cells, and subjecting said suspension to centrifugation, does not reasonably provide enablement for said method of forming hESC aggregates wherein said method comprises a suspension of individual separate hESCs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

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The breadth of the claimed invention encompasses a suspension of hESC that are all individually separate without any clumping or the combination of two or more cells, that are then used to form hESC aggregates using the claimed method.

Whereas the nature of the invention is the centrifugation of a hESC suspension, comprising both clumps and single cells, to form an aggregation of hESCs, the art teaches that a hESC suspension that comprises only individually separate hESC is unpredictable.

A review of the working examples in the specification however does not provide support for a suspension of hESCs that is comprised wholly of individually separate cells.

Working Examples

Regarding a suspension of hESCs, the specification teaches on pg. 22 lines 3-6 that hESCs were collected, centrifuged at 1500 rpm for 2 minutes and then gently re-suspended in 3-5 mls of differentiation medium and then a cell count was then performed. There is no other teaching in the specification that would indicate that the cells in the suspension, which were counted, were individually separate as claimed. Applicant's in their arguments (6/7/2011) allege that by performing a cell count on said suspension that the skilled artisan would readily recognize that the suspended hESCs would need to be individually separate, i.e. no clumps (pg. 7 last parag.).

As set forth above the instant claims encompass a suspension of hESCs that comprises no clumps and consists only of individually separate hESCs. However, a suspension of individually separate hESC is unpredictable in view of the teachings in the art below.

Teachings in the Art

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For example Watanabe et al. teach that hESC suffer from poor survival after cell dissociation due to an increase in dissociation-induced apoptosis (see Abstract, 2007, Nature Biotechnology, Vol. 25(6), pgs. 681-686). Watanabe continues to teach that hES cells undergo massive cell death upon cellular detachment and dissociation and are difficult if not impossible to use when dissociated (pg. 681 col. 1 parag. 1 lines 9-14).

Regarding obtaining a suspension of individually separate hESCs, the art teaches that this also is unpredictable. For example Thomson et al. (1998, Science, Vol. 282(6), pgs. 1145-1147) that cultures of hESCs, when mechanically dissociated with a micropipette, still resulted in clump sizes of 50 to 100 cells (pg. 1147 col. 2 last 5 lines bridge col. 3 lines 1-5).

Reubinoff et al. (2000, Nature Biotechnology, Vol. 18, pgs. 399-404) also obtained results similar to Thomson regarding clumps in suspensions of hESCs and further teaches the difficulty of working with single hESCs. For example, Reubinoff teaches that their cultures of hESCs, when subjected to mechanical pipetting, resulted in clumps of ~100 cells (pg. 403 col. 2 parag. 1). Reubinoff continues to teach that growth from small clumps of hESCs (<10) was not possible (pg. 399 col. 2 last parag. lines 9-13) and that aggregates of hESCs in standard medium without feeder cells resulted in considerable cell death (pg. 401 col. 2 parag. 1 lines 1-3).

Conclusion

Again it is maintained that the breadth of the claimed invention encompasses a cell suspension of only individually separate hESC with no clumping. While Applicant's allege that use of a cell counter in the working examples infers that only individually separate hESCs are present in a suspension of hESCs, the art teaches that such a suspension would be unpredictable

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since 1) clumps will also be present even following pipetting and 2) hESC undergo massive cell death when dissociated.

While it is conceivable that the suspension comprises both clumps and individual hESCs, it is untenable that Applicant can obtain a suspension of hESCs that comprises no clumps at all by merely pipetting a suspension of hESCs. Further it is fully appreciated that the skilled artisan would, when performing a cell count, want to minimize the number of cells clumps to obtain an approximate cell count. However the skilled artisan is also fully capable of performing and obtaining an approximate cell count while some clumps of hESCs remain in suspension.

Thus, in view of the teachings in the art above and the teachings in the specification, the skilled artisan would not find the claimed invention enabled for its entire breadth. At a minimum the claimed invention is enabled for a suspension of hESCs that comprises both clumps of hESCs and individual hESCs.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 41-56 and 58-66 are rejected under 35 U.S.C. 102(e) as being anticipated by Price et al. (US 2002/0076747 A1, published 6/20/2002). As evidenced by Leshem et al. (1990, J. Exp. Med., Vol. 171, pgs. 1057-1071).

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Regarding claims 47-49 and 62-66, which are drawn to centrifugation using low-attachment centrifugation plates or holding vessels, wherein said vessels are round bottom wells or conical shaped wells, these claims would be obvious as a matter of design choice and one would be motivated to use said plates or vessels since they are readily available and applicable to methods of centrifuging cells. For example at the time of filing, Leshem et al. teaches that low-attachment holding vessels comprising either round or conical wells (Nunc 96) were available for use regarding cell aggregates (see pg. 1058, parags. 7 and 8).

Applicants assert in their amendment filed on 6/7/2011 that "The cell count can only be determined once the hESCs are suspended as individual cells and one skill in the art would readily recognize this" (pg. 7 last parag.). Accordingly, prior art that would perform a cell count of hESCs prior to centrifugation would then inherently have obtained a suspension of individual separate hESCs.

Regarding claims 41 and 42, Price teaches a method of forming ES cells aggregates by passaging and performing a cell count on ES cells (pg. 13 parag. 0141 lines 1-2), therefore as asserted by Applicant obtaining a suspension of individual separate ES cells, which are then pelleted following said passaging (pg. 8 parag. 0104). Price continues to teach that their ES cells can be human ES cells (pg. 8 parag. 0102, line 3).

Regarding claims 43-46, Price teaches that to prior to aggregation of ES cells, they are dissociated using a combination of trypsin and EDTA (pg. 8 parag. 0104, lines 3-5).

Regarding claim 50, Price teaches ES cell aggregates were then re-plated in growth medium which improved ES cell morphology within two days of growth (pg. 13 parag. 0141 lines 3-5).

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Regarding claims 51 and 52, Price teaches that ES cell aggregates can be cultured in the presence of one or more growth factors which will cause ES cells to differentiate into the cell type of interest (pg. 10 parag. 0115, last 3 lines), which include red blood cells (pg. 10 parag. 0117, line 7).

Regarding claim 53, Price teaches that differentiated cells (from ES cells) can be isolated and then delivered to a mammal (pg. 2 parag. 0024 last 3 lines).

Regarding claim 54, Price et al. teach a method of forming hES cell aggregates comprising:

- obtaining a suspension of hES cells (pg. 12 parag. 0129);
- growing the hES cells on a culture medium (pg. 12 parag. 0130 lines 1-10);
- harvesting the hES cells from the medium (pg. 12 parag. 0130),
- suspending the harvested hES cells in a serum-free medium (pg. 12 parag. 0130 last four lines); and
- centrifuging said suspended cells (pg. 8 parag. 0104).

Regarding claim 55, Price teaches the mouse embryonic fibroblasts can be used to support the culture medium (pg. 8 parag. 0106).

Regarding claim 56, the ordinary artisan would find the claim method of growing the hESC's to 60-80% confluency obvious, so as to avoid differentiation of hESC aggregates into specific cell types. It was well accepted in the art at the time of filing that as hESC culture approaches 100% confluency, peripheral differentiation occurs.

Regarding claim 57 limiting the centrifugation step to 1,500 rpm.

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Regarding claim 58, Price teaches that the ES cells were re-suspended in absence of growth factors (pg. 12 parag. 0130, last 4 lines),

Regarding claim 59, Price teaches that the hES cells were counted (pg. 13 parag. 0141 lines 1-4).

Regarding claim 60, Price teaches that the hES cells were dissociated with trypsin (pg. 12 parag. 0130).

Regarding claim 61, Price teaches that EDTA was used with trypsin (pg. 12 parag. 0129).

Thus the cited teachings of Price clearly anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 54 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (US 2002/0076747 A1, published 6/20/2002) and Studer et al. (US 2003/0036195, published 2/20/2003).

Price et al. teach a method of forming hES cell aggregates comprising:

obtaining a suspension of hES cells (pg. 12 parag. 0129);

growing the hES cells on a culture medium (pg. 12 parag. 0130 lines 1-10);

harvesting the hES cells from the medium (pg. 12 parag. 0130),

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suspending the harvested hES cells in a serum-free medium (pg. 12 parag. 0130 last four lines); and

centrifuging said suspended cells (pg. 8 parag. 0104).

Price et al. do not teach centrifuging the harvested hES cells at 1500 rpm for 2 minutes at 4° C.

However one of ordinary skill in the art would find it obvious to centrifuge at those parameters.

For example Studer et al. teach a method of forming nuclear transfer (nt) ES cell aggregates comprising harvesting the ES cells from culture medium, re-suspending said ES cells in serum-free medium and centrifuging said cells at 1500 rpm for 5 minutes at 4° C (pg. 10 parag. 0089 lines 1-8).

With regard to the limitation of claims 57, wherein the time of centrifugation is 2 minutes, it should be noted that such a time limit is within the scope of routine experimentation and optimization in the prior art. Applicants should further note that as indicated in MPEP 2144.05: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Thus at the time of filing the ordinary artisan would have found it prima facie obvious to combine the teachings of Price regarding a method of forming hES cell aggregates with the teachings of Studer regarding a method of forming ES cell aggregates using specific

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centrifugation conditions since both methods are drawn to forming ES cell aggregates using centrifugation. One of ordinary skill in the art would have been motivated to make such a combination since Studer provides specific rpm, time and temperature parameters for which to guide the ordinary artisan to form ES cell aggregates. There would have been a reasonable expectation of success that centrifuging ES cells at 1500 rpm, for several minutes at 4° C would form ES cell aggregates since the mere fact of centrifuging suspended ES cells will cause them to aggregate.

Thus the cited art provides the requisite teachings and motivations to make and use the invention as claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID A. MONTANARI whose telephone number is (571)272-3108. The examiner can normally be reached on Mon-Wed 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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